

- (II) Claims 12 and 14-16 drawn to a pharmaceutical composition that will be examined with whichever drug is elected in claim 1.
- (III) Claim 13 drawn to the compounds of claim 1, plus an additional active ingredient. According to the Examiner the presence of an additional active ingredient in this claim makes the claim of a different scope than claim 1.
- (IV) Claims 18-29 drawn to multiple methods of using the above compounds. The Examiner states that only one method of using the compound will be examined with whichever compound is elected, and a specific disease is required to be elected.
- (V) Claim 30 drawn to the process of actually making the composition. According to the Examiner, the process is old and well known.

In response to the restriction requirement, Applicants elect group I, i.e., claims 1-11, directed to the prodrug product of these claims, wherein the specific anti-proliferative drug is methotrexate, and wherein the specific method of use is for treatment of a disease or disorder relating to uncontrolled cell growth, and the method of manufacture is as claimed in claim 30. However, Applicants make this election with traverse, as set forth below.

Applicants respectfully submit that the Examiner's determination of groupings is overly restrictive and submit that the claims meet the unity of invention criteria as set out in Patent Cooperation Treaty Rule 13.2. PCT Rule 13.2 states that the requirement of unity of invention is fulfilled where there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. The term "special technical features" is then further defined as "a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." Applicants assert that all of the claims of record have the same or corresponding special technical feature, namely the pro-drug structure of general formula I as described in claim 1. It is respectfully submitted that, since this special technical feature is found in each of the claims and this special technical feature makes a contribution over the prior art, all of the claims comply with the requirement of unity of invention.

In the case of groups I and II, the claims of these groupings are all in the same category of invention, i.e., a product, and comprise the same common feature that defines a contribution over the prior art, i.e., the pro-drug structure of general formula I as described in claim 1. The only difference between groups I and II are the addition of a pharmaceutically acceptable carrier (claim 12) and specified forms of administration of the composition (claims 14-16). Regardless of the additions in claims 12 and 14-16, however, these claims still have the same or corresponding special technical feature as the claims of group I. Moreover, as set forth in M.P.E.P. § 1850, “If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims.” Accordingly, it is respectfully submitted that, despite the addition of additional elements in the claims of group II, there is unity of invention for the claims of groups I and II.

In addition, the Examiner contends that claim 13 forms its own group (group III) because the claim has an additional active ingredient and is, therefore, of different scope. Applicants respectfully submit that this difference in claim scope is irrelevant and that unity of invention is not lost due to the presence of an additional active ingredient, so long as the same special technical feature is present, i.e., the pro-drug of general formula I as described in claim 1. As set forth above, M.P.E.P. § 1850 specifically states that, if the independent claims avoid the prior art and satisfy the requirement of unity of invention, there is lack of unity of invention for claims that depend from the independent claims. Moreover, contrary to the Examiner’s position, the M.P.E.P. explicitly states that “it does not matter if a dependent claim itself contains a further invention.” Accordingly, it is clear that the presence of an additional active ingredient in claim 13, and the resulting difference in claim scope, does not result in loss of unity of invention, and Applicants request that this rejection be withdrawn.

Furthermore, Applicants respectfully submit that the claims of group IV also have unity of invention with the claims of groups I, II and III because they, too, have the same special technical feature. In addition, although the claims of group IV are of a different category (process of use) than the claims of groups I, II and III (product), 37 C.F.R. § 1.475(b) states that a product and a process of use of that product will be considered to have unity of invention.

However, because the claims of group IV contain three separate methods of use, Applicants choose the third method of use, i.e., claims 23-29, a method of use of the product of Group II for treatment of a disease or disorder relating to uncontrolled cell growth, for prosecution in this application, along with the product claims of groups I, II and III, which as discussed above should be contained in a single grouping. Accordingly, because claims 23-29 from within group IV are directed to a method of use of the product of Group II, there is unity of invention between these claims, and Applicants request that this rejection be withdrawn.

With respect to claim 30, Group V, Applicants respectfully assert that this claim should be examined with the claims of groups I, II, III and IV. As set forth in 37 C.F.R. § 1.475(b) and as stated by the Examiner, a product, a process for the manufacture of that product and use of that product will be considered to have unity of invention. In addition, the claim (30) of group V meets the criteria of PCT Rule 13.2 in that it also comprises the same special technical feature as the claims of groups I, II, III and IV, namely the pro-drug of general formula I as described in claim 1. Accordingly, because claim 30 (group IV) is directed to a method manufacture of a medicament comprising the product of Group I, there is unity of invention between these claims, and Applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of the claims of Groups I, II, III, IV (at least claims 23-29) and V have unity of invention for the reasons indicated above and that Applicants are entitled to have all these claims examined together on the merits. Although Applicants have made a provisional election above, Applicants respectfully urge that the Examiner reconsider his rejections and withdraw his restriction requirement. In any case, Applicants will make an appropriate amendment canceling claims or amending claims to delete portions directed to non-elected inventions after the Examiner has considered and acted upon Applicants' arguments herein.

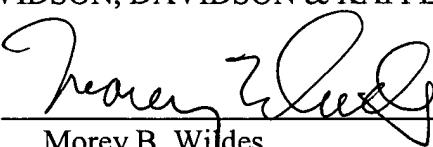
According to currently recommended U.S. Patent and Trademark Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview would advance the prosecution of the case. In particular, in the event that a discussion between the Examiner and an attorney for Applicants would assist in overcoming the restriction

requirement, the Examiner is requested to contact the undersigned in order to conduct a telephone interview.

Reconsideration of the present application, as amended, is requested. Applicants respectfully submit that all the claims pending in this application are patentable. An early and favorable action on the merits is earnestly solicited.

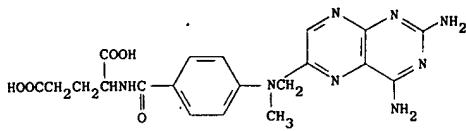
Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By:


Morey B. Wildes
Registration No. 36,968

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
(212) 736-1940

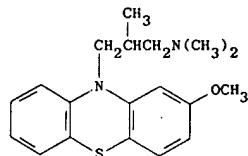
5908. Methotrexate. *N*-[4-[(2,4-Diamino-6-pteridinyl)methyl]methylamino]benzoyl-L-glutamic acid; 4-amino-N¹⁰-methylpteroylglutamic acid; 4-amino-10-methylfolic acid; methylaminopterin; amethopterin; MTX; Cl-14377; Emtexate; A-Methopterin; Rheumatrex. C₂₀H₂₁N₉O₅; mol wt 454.46. C 52.86%, H 4.88%, N 24.66%, O 17.60%. A folic acid antagonist. Prepn: Seeger *et al.* *J. Am. Chem. Soc.* 71, 1753 (1949). Metabolism: Freeman, *J. Pharmacol. Exp. Ther.* 122, 154 (1958); Henderson *et al.* *Cancer Res.* 25, 1008, 1018 (1965). Toxicity studies: Condit *et al.* *Cancer* 13, 222-249 (1960); *ibid.* 23, 126 (1969). Pharmacokinetic models: Bischoff *et al.* *J. Pharm. Sci.* 59, 149 (1970); *idem*, *ibid.* 60, 1128 (1971). Comparative study in treatment of acute lymphocytic leukemia in children: A. I. Freeman *et al.* *N. Engl. J. Med.* 308, 477 (1983). Short-term efficacy in rheumatoid arthritis: M. E. Weinblatt *et al.* *ibid.* 312, 818 (1985). Toxicity data: H. R. Scherf *et al.* *Arzneimittelforsch.* 20, 1467 (1970). Comprehensive description: A. R. Chamberlin *et al.* in *Analytical Profiles of Drug Substances* vol. 5, K. Florey, Ed. (Academic Press, New York, 1976) pp 283-306. Review of metabolism and pharmacokinetics: W. E. Evans, *Appl. Pharmacokinet.* 1980, 518-548. Review of clinical pharmacology: J. R. Bertino, *Cancer Chemother.* 3, 359-375 (1981); J. Jolivet *et al.*, *N. Engl. J. Med.* 309, 1094-1104 (1983). Symposium on clinical experience in rheumatoid arthritis: *J. Rheumatol.* 12, Suppl. 12, 1-44 (1985).



Monohydrate, yellow crystals from dil HCl, dec 185-204° (bath preheated to 160°). uv max (0.1N HCl): 244, 307 nm; (0.1N NaOH): 257, 302, 370 nm. Soluble in alkaline solns with decompn. LD₅₀ i.v. in rats: 14 mg/kg (Scherf).

Disodium salt, C₂₀H₂₀N₈Na₂O₅, *Folex*, *Mexitate*.
THERAP CAT: Antineoplastic; antirheumatic.

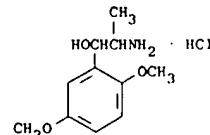
5909. Methotripeprazine. 2-Methoxy-N,N, β -trimethyl-10H-phenothiazine-10-propanamine; 10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine; 2-methoxy-10-(2-methyl-3-dimethylaminopropyl)phenothiazine; 3-methoxy-10-(3-dimethylamino-2-methylpropyl)phenothiazine; levomeprazine; 2-methoxytrimeprazine; levomeprazine; RP 7044; Sinogan-Debil; Tisercin; Neozine; Nirvan; Nozinan; Levoprome. C₁₉H₂₄N₂O₅; mol wt 328.46. C 69.47%, H 7.36%, N 8.53%, O 4.87%, S 9.76%. Prepn: Courvoisier *et al.*, *C.R. Soc. Biol.* 151, 1378 (1957); Jacob, Robert, *U.S. pat.* 2,837,518 (1958 to Rhône-Poulenc).



Maleate, C₂₃H₂₈N₂O₅S. *Minozinan*, *Milezin*, *Neuractil*, *Neurocil*, *Sofmin*, *Veracil*. Crystals, darkened by light. Dec about 190°. The free base is levorotatory: [α]_D²⁰ -17° (c = 5 in chloroform). The maleate is sparingly sol in water (0.3% at 20°) and in ethanol (0.4%). pH of a 0.3% aq soln is 4.3. THERAP CAT: Analgesic.

5910. Methoxamine Hydrochloride. α -(1-Aminoethyl)-2,5-dimethoxybenzenemethanol hydrochloride; α -(1-aminoethyl)-2,5-dimethoxybenzyl alcohol hydrochloride; 2-amino-1-(2,5-dimethoxyphenyl)-1-propanol hydrochloride; β -hydroxy- β -(2,5-dimethoxyphenyl)isopropylamine hydrochloride; β -(2,5-dimethoxyphenyl)- β -hydroxyisopropylamine hydrochloride; 2,5-dimethoxynorephedrine hydrochloride; Pressomin Hydrochloride; Vasoxine Hydrochloride; Vasoxy Hydrochloride; Vasylox Hydrochloride. C₁₁H₁₈ClNO₃; mol wt 247.71. C 53.33%, H 7.32%, N 5.66%, Cl 14.31%, O

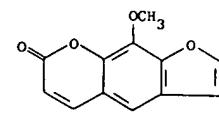
19.38%. Prepn: Baltzly *et al.* *U.S. pat.* 2,359,707 (1944 to Burroughs Wellcome).



Crystals, mp 212-216°. Very sol in water. One gram dissolves in 2.5 ml water, in 12 ml ethanol. Practically insol in ether, benzene, chloroform. pH of a 2% aq soln between 4.5 and 5.5.

THERAP CAT: Adrenergic (vasopressor).

5911. Methoxsalen. 9-Methoxy-7H-furo[3,2-g][1]benzopyran-7-one; 6-hydroxy-7-methoxy-5-benzofuranacrylic acid δ -lactone; 9-methoxysoralen; 8-methoxy-4',5':6,7-furocoumarin; 8-methoxyfuran-3',2':6,7-coumarin; ammodin; xanthotoxin; 8-methoxysoralen; 8-MOP; 8-MP; Meladine; Meloxine; Methoxa-Dome; Oxsoralen Ultra; Psoralon-MOP. C₁₂H₈O₄; mol wt 216.18. C 66.67%, H 3.73%, O 29.60%. Naturally occurring analog of psoralen, q.v., found in spp. of *Leguminosae*, *Umbelliferae*, and *Rutaceae*. Isolation: Priess, *Ber. Deut. Pharm. Ges.* 21, 227 (1911); Thoms, *Ber.* 44, 3325 (1911); 45, 3705 (1912); Jois *et al.*, *J. Indian Chem. Soc.* 10, 41 (1933); Späth *et al.*, *Ber.* 73, 1361 (1933); Schonberg, Sina, *Nature* 160, 468 (1947); 161, 481 (1948); *J. Am. Chem. Soc.* 72, 4826 (1950). Synthesis: Späth, Pailer, *Ber.* 69, 767 (1936); Lagercrantz, *Acta Chem. Scand.* 10, 647 (1956); Stanley, Vannier, *U.S. pat.* 2,889,337 (1959 to USDA); P. Nore, E. Honkanen, *J. Heterocycl. Chem.* 17, 985 (1980). Use in treatment of psoriasis and mycosis fungoidea: J. A. Parrish *et al.*, *Int. J. Dermatol.* 19, 379 (1980). Acute toxicity data: Hakim *et al.*, *J. Pharmacol. Exp. Ther.* 131, 394 (1961). Phototoxicity study: A. Kornhauser *et al.*, *Science* 217, 733 (1982). Comprehensive description: M. A. Loufty, M. A. Hassan, in *Analytical Profiles of Drug Substances* vol. 9, K. Florey, Ed. (Academic Press, New York, 1980) pp 427-454. Review of use in phototherapy: T. F. Anderson, J. J. Voorhees, *Ann. Rev. Pharmacol. Toxicol.* 20, 235-258 (1980); *Acta Derm. Venereol. Suppl.* 106, 9-42 (1982).



Silky needles from hot water or benzene + petr ether, long rhombic prisms from alcohol + ether. mp 148°. Odorless. Bitter taste followed by tingling sensation. pH 5.5. uv max: 219, 249, 300 nm (log ε 4.32, 4.35, 4.06). Practically insol in cold water; sparingly sol in boiling water, liq petroleum, ether. Sol in boiling alcohol, acetone, acetic acid, vegetable fixed oils, propylene glycol, benzene. Freely sol in chloroform. Sol in aq alkalies with ring cleavage, but is reconstituted upon neutralization. LD₅₀ i.p. in rats: 470 ± 30 mg/kg (Hakim).

THERAP CAT: Pigmentation agent.

5912. Methoxyamine. *O*-Methylhydroxylamine; methoxyamine; α -methylhydroxylamine; hydroxylamine methyl ether. CH₃NO; mol wt 47.06. C 25.52%, H 10.71%, N 29.77%, O 34.00%. CH₃ONH₂. Prepd by treating hydroxylamine disulfonic acid with methyl sulfate: Goldfarb, *J. Am. Chem. Soc.* 67, 1852 (1945). May also be prepd from hydroxyurethan.

Free base. *Highly poisonous!* Mobile liquid. Fishy, amine odor. bp₇₆₀ 49-50°. Miscible with water, alcohol, ether.

Hydrochloride, CH₃ONH₂·HCl, nacreous scales from alcohol + ether, m.p.

Picrate, mp 175°

USE: Analytical addition of metho the rearrangement